147

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,987	TOWNSEND ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *10,19-36,41 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11-18 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 3/19/04, has been entered.
Claims 2-4, 6-7 and 13 have been amended.
Claims 37-42 have been added.

Claims 1-42 are pending.

For the record, applicant's election with traverse of Group I and the species of agent one is soluble CTLA4, the species of agent two is anti-CD154 antibody and the species of agent 3 is anti-LFA-1 antibody in Paper No. 11 and the species of cardiac allografts in the communication filed 7/22/03 has been acknowledged.

Therefore, claims 1-9, 11-18 and newly added claims 37-40 are under consideration as they read on the elected invention and species indicated above in the instant application.

Claims 10, 19-36 and newly added claims 41-42 are withdrawn from consideration as being drawn to the nonelected invention and species.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 3/19/04.
The rejections of record can be found in the previous Office Action.

3. Applicant's comment that the deposit of biological materials under 35 USC 112, first paragraph, has been satisfied is acknowledged.

Applicant is reminded that applicant has submitted that the referenced biological materials (e.g. claims 6, 8, 11) are commercially available. At this time, it appears that requirements for the deposit of biological materials under 35 U.S.C. § 112, first paragraph, are satisfied for the claimed biological materials

For the record, it is maintained that the referenced biological materials are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas / plasmids which produce these referenced biological materials. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

4. Claim 1, 2, 5-9, 11-17 and 38-40 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 2, 5-9 ,11-17 and 38-40 are indefinite in its recitation of "regulating" because it is ambiguous as to the nature, direction (e.g. positive or negative) or degree of said "regulating".

Applicant should amend the claims to recite a clear and definite endpoint (e.g. inhibiting).

Applicant's arguments, filed 3/19/04, have been fully considered but are not found convincing for the reasons of record.

Applicant asserts that the specification defines the word "regulate" as meaning "to inhibit or stimulate a response".

Applicant's reliance on the completely opposite endpoints of "inhibiting" and "stimulating" supports the rejection of record, as the claims fail to particularly point out and distinctly claim the subject matter. It is confusing that the same reagents in the same methods can result in completely opposite endpoints.

Applicant's arguments are not found persuasive.

B) Claim 40 contains the trademark or trade name "etanercept" and "anakinra". Where a trademark or trade name is used in a claims as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 USC 112, second paragraph, See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark or the trade name "etanercept" and "anakinra" is used to identify or describe an immunosuppressive agent, and accordingly, the identification or the description is indefinite. The relationship between a trademark or tradename and the product it identifies may be uncertain and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark or tradename.

C) Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

5. Claims 1-7, 9, 12-18 and newly added claims 37-40 are rejected under 35 U.S.C. § 102(e) as being anticipated by Digan et al. (US 2002/0142000 A1) (see entire document, including claims, particular claim 28) for the reasons of record.

Applicant's arguments, filed 3/19/04, have been fully considered but are not found convincing for the reasons of record.

Applicant asserts that a pending application for patent will be considered prior art only as of its filing date, if the application is filed by 11/29/00 and that if a patent application is filed before 11/29/00, then it becomes available as prior art only as of its publication date.

In contrast to applicant's assertions, the filing date of the application is no longer relevant in determining what version of 35 USC 102(e) to apply in determining the patentability of that application or the patent resulting from that application. See MPEP 706.02(f) and 2136. In particular, see the Revised 35 USC 102(e), as amended by the AIPA (Pub. L. 106-113 113 Stat. 1501 (1999) and as further amended by the Intellectual Property and High Technology Technical Amendments Act of 2002 (Pub. L. 107-273, 116 Stat. 1758 (2002).

A person shall be entitled to a patent unless --
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Therefore, the prior art of record stands as a rejection under 35 U.S.C. § 102(e).

Digan et al. teach the use of anti-CD3 immunotoxins in combination with other pharmaceutical agents effective in treating various T cell mediated disorders, including acute or chronic transplant rejection, including CTLA4-Ig, anti-LFA-1 antibodies and anti-CD40 ligand antibodies (see Therapeutic Uses of Recombinant Anti-CD3 Immunotoxins on pages 12-16, including paragraph 0198 on pages 12-13). Here, Digan et al. teach various modes of administration, including separate overlapping and systemic administration. Although Digan et al. does not disclose the specific deposited materials comprising CTLA4Ig recited in claim 6, the referenced CTLA4Ig would have had the inherent properties of the CTLA4Ig produced by the deposited materials recited in claim 6.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods to inhibit graft rejection in transplant patients with a combination of anti-CD3 immunotoxins in combination including CTLA4-Ig, anti-LFA-1 antibodies and anti-CD40 ligand antibodies.

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure

6. Claims 1-9, 12-18 and newly added 37-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320) (1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456).

Applicant's arguments, filed 3/19/04, have been fully considered but are not found convincing for the reasons of record.

While applicant acknowledges that the prior art describes each of the three agents recited in the claimed methods, applicant argues that there is no evidence showing that the references suggest the claimed invention, particularly the combination of at least three agents.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the prior art references teach the advantages of combining immunosuppressive agents that target discrete targets to increase the efficacy of immunosuppression and to decrease the toxicity of immunosuppressive regimens. The teachings of the prior art references indicating success in combining immunosuppressive agents to address these known issues and endpoints would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve such well known problems in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

In contrast to applicant's assertions, the following of record is reiterated for applicant's convenience.

Blazar et al. teach methods of inhibiting antigen specific T cell responses, including inhibiting organ graft rejection, including cardiac transplant (see overlapping paragraph on pages 7-8, Tissue and Organ Transplantation on pages 23-24), with first agent which is an inhibitor of costimulatory signal together with a second agent which inhibits the generation of a delivery proliferative signal in the T cell (see entire document, including Detailed Description of the Invention and the Claims). Blazar et al. teach that the with first agent which is an inhibitor of costimulatory signal , including CTLA4 and anti-LFA-1 antibody as the second agent which inhibits the generation of a delivery proliferative signal in the T cell (See Summary of

the Invention on pages 2-4; Detailed Description of the Invention, including pages 6-8, including Bone Marrow Transplantation - Inhibition of GVHD on pages 22-23; Tissue and Organ Transplantation on pages 23-24; and Claims). In addition, Blazar et al. teach treating a variety of subjects (page 19, lines 30-32) in a variety of known modes of administration in effects amounts to achieved the desired result (see Compositions on pages 21 and Uses of the Invention on pages 21-24).

Blazar et al. differs from the claimed invention by not disclosing the combination of a third inhibitor of CD40 ligand interactions in methods of inhibiting transplant rejection. It is noted that Blazar et al. does teach targeting gp39 (page 8, line 6), which is the CD40 ligand.

Larsen et al. teach methods of inhibiting immune responses by blocking CD40L/CD40 and CTLA4/CD28/B7 pathways ,including inhibiting transplant rejection and cardiac allografts (column 6, paragraphs 4, 7), including the combination of CTLA4 and anti-CD40 ligand antibody (e.g. MR1) (see Detailed Description of the Invention (e.g. see columns 5-10 and Examples on columns 10-18) (see entire document). Larsen et al. teach the advantages of inhibiting or blocking both CTLA4/B7 and CD40L/CD40 pathways in promoting prolonged immunosuppression (see column 10, paragraph 3 and Discussion on columns 18-19). Larsen et al. teach treating in a variety of subjects (column 8, paragraph 6) in a variety of known modes of administration depending on the location of the tissue or disease being treated as well as the severity and course of the medical disorder in the judgment of the treating physician (see columns 9-10).

In addition to the teachings of Blazar et al. and Larsen et al., it was known at the time the invention was made that the use of immunosuppressive therapy relies upon a number of basic principles as set forth in Strom et al. These principles include that different agents are used, each of which is directed at a different molecular target and aimed at interrupting several discrete stages in the immune activation pathway (e.g. see page 451 and Figure 36.1). Also, additive-synergistic effects are achieved through the application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agents while increasing the total immunosuppressive effect (see page 451, column 1, paragraph 2).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Larsen et al. to those of Blazar et al. to obtain a combining CTLA4Ig and anti-CD40 ligand antibodies, given their increased immunosuppressive properties, to the Blazar's second agent anti-LFA-1 antibodies which inhibits the generation of a delivery proliferative signal in the T cell to increase the efficacy of immunosuppression in therapeutic regimens to promote the long term survival of transplants, including cardiac allografts at the time the invention was made. According to Blazar et al., Larsen et al. and Strom et al., a person of ordinary skill in the art would have been motivated to combine immunosuppressives to produce an increased immunosuppressive regimen in promoting graft survival at the time the invention was made. In addition to the evidence and expectation of success in combining immunosuppressive agents, including those claimed, the use of combination therapy with biologicals would have had the expected advantage of reducing the toxicity of immunosuppressive regimens associated with transplantation at the time the invention was made, as taught by Strom et al.

A person of ordinary skill in the art would have recognized that the combination of three immunosuppressive agents such as CTLA4Ig, anti-CD40 ligand antibodies and anti-LFA-1 antibodies discussed by the references above would have had advantages of increased immunosuppression and decreased toxicity in achieving antigen-specific nonresponsiveness in promoting long terms survival of transplanted tissues and organs at the time the invention was made. Given the referenced and art known modes of administration at the time the invention was made, the ordinary artisan would have administered the agents locally or systemically as well as sequentially or concurrently given the nature of the grafted tissue or organ and the needs of the patient. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Larsen et al. to those of Blazar et al. to obtain a combining CTLA4Ig and anti-CD40 ligand antibodies, given their increased immunosuppressive properties, to the Blazar's second agent anti-LFA-1 antibodies which inhibits the generation of a delivery proliferative signal in the T cell to increase the efficacy of immunosuppression in therapeutic regimens to promote the long term survival of transplants, including cardiac allografts at the time the invention was made. According to Blazar et al., Larsen et al. and Strom et al., a person of ordinary skill in the art would have been motivated to combine immunosuppressives to produce an increased immunosuppressive regimen in promoting graft survival at the time the invention was made. In addition to the evidence and expectation of success in combining immunosuppressive agents, including those claimed, the use of combination therapy with biologicals would have had the expected advantage of reducing the toxicity of immunosuppressive regimens associated with transplantation at the time the invention was made, as taught by Strom et al.

A person of ordinary skill in the art would have recognized that the combination of three immunosuppressive agents such as CTLA4Ig, anti-CD40 ligand antibodies and anti-LFA-1 antibodies discussed by the references above would have had advantages of increased immunosuppression and decreased toxicity in achieving antigen-specific nonresponsiveness in promoting long terms survival of transplanted tissues and organs at the time the invention was made. Given the referenced and art known modes of administration at the time the invention was made, the ordinary artisan would have administered the agents locally or systemically as well as sequentially or concurrently given the nature of the grafted tissue or organ and the needs of the patient. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claims 6, 8 and 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320)(1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230)and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) as applied to claims 1-9, 12-18 and 37-40 above and further in view of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40L antibodies and anti-LFA-1 antibodies, as acknowledged on pages 15-16 of the instant specification and cited in published references).

Applicant's arguments, filed 3/19/04, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above, particularly with respect to over Blazar et al. (WO 95/34320)(1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456).

8. Claims 1-9, 11-18 and newly added claims 37-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Digan et al. (US 2002/0142000 A1) (see entire document, including claims, particular claim 28) in view of Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) and of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40L antibodies and anti-LFA-1 antibodies, as acknowledged on pages 15-16 of the instant specification and cited in published references) for the reasons of record.

Applicant's arguments, filed 3/19/04, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above, particularly with respect to over the prior art status of Digan.

9. No claim allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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